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## Chapter 50: Alzheimer Disease

# INTRODUCTION

- *Alzheimer disease* (AD) is the most common cause of dementia with unknown etiology. It affects about 6.9 million Americans aged 65 and older. By 2050, this number is expected to double.

# CLINICAL PRESENTATION

- Cognitive impairment and memory loss are not normal signs of aging.
- Initial memory complaints may be vague, or friends and family might note the patient is "forgetful." Cognitive decline is usually gradual throughout the illness. Moderate stages often include behavioral disturbances. In advanced stages, loss of daily functions like dressing, bathing, and toileting is common. **Table 50-1** shows the stages of AD.

TABLE 50-1

**Stages of Alzheimer Disease**

| | |
|---|---|
| Mild (MMSE score 26–21) | The patient struggles to remember recent events. Their ability to manage finances, prepare food, and do household tasks declines. They may get lost while driving, start withdrawing from challenging tasks, and give up hobbies. The patient might also deny having memory problems. |
| Moderate (MMSE score 20–10) | The patient needs help with daily activities and is often disoriented about time, like the date, year, or season. Recall of recent events is severely impaired. They may forget past event details and names of family and friends, with daily functioning varying. The patient usually denies issues but may become suspicious or tearful. They lose the ability to drive safely, and agitation, paranoia, and delusions are common. |
| Severe (MMSE score 9–0) | The patient loses the ability to speak, walk, and feed themselves and becomes incontinent. They require 24/7 care. |

MMSE, Mini-Mental State Examination.

# DIAGNOSIS

- AD is a spectrum starting with an asymptomatic preclinical phase, progressing to symptomatic preclinical, and then to dementia. It's clinically diagnosed, primarily based on symptoms and difficulties with daily activities as reported by patient and caregiver interviews.
- Patients suspected of having AD should undergo a history and physical exam with lab tests, such as serum $B_{12}$, folate, thyroid panel, blood cell counts, serum electrolytes, and liver function tests.

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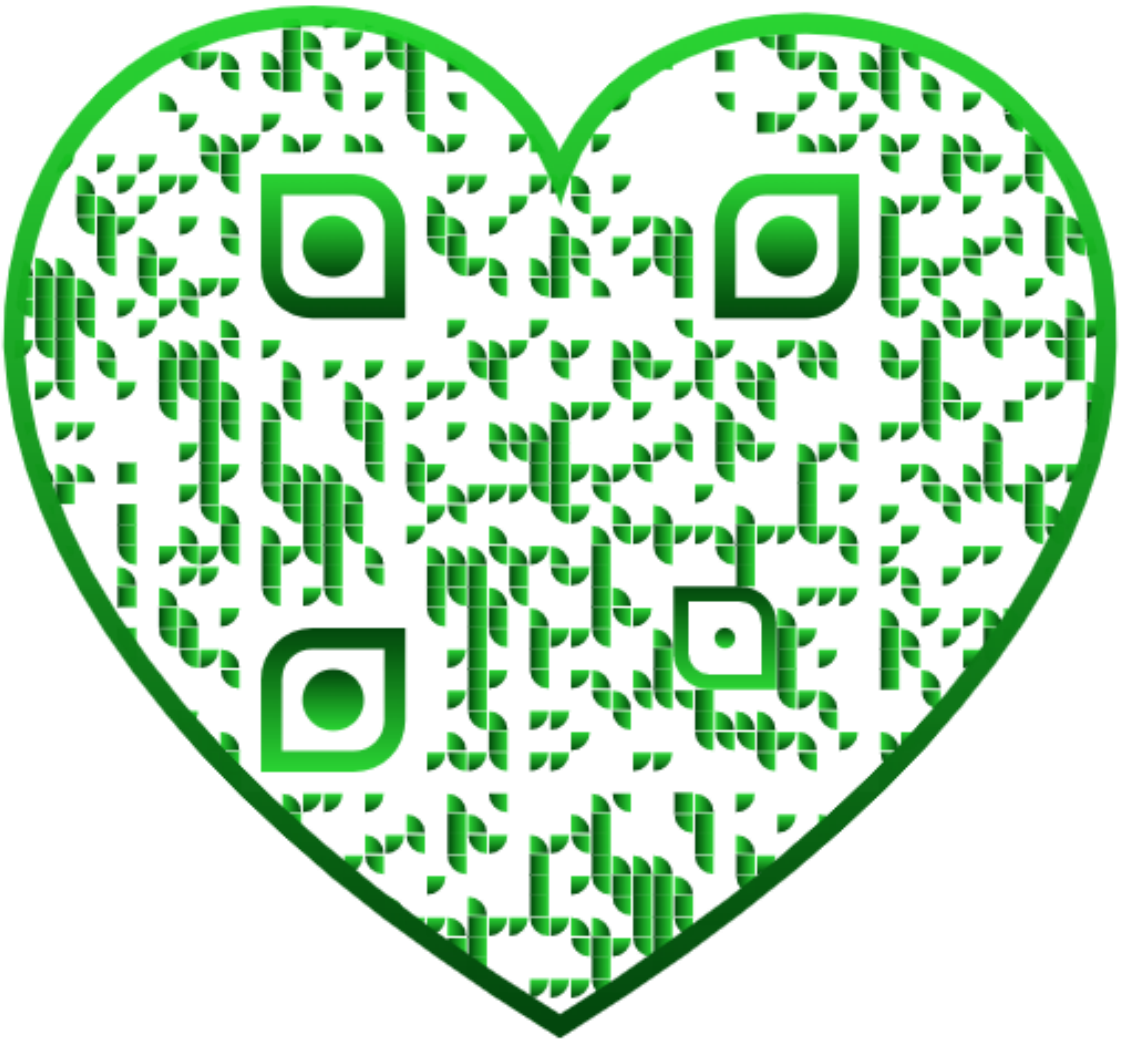

- Full neuropsychiatric testing, the use of either positron emission tomography (PET) imaging and/or cerebral spinal fluid (CSF) testing, and apolipoprotein (*APOE)* genotyping are required to confirm the diagnosis and determine qualification for newer treatments.
- Gather information on medication and substance use, family medical history, and any history of trauma, depression, or head injury. Rule out medications such as anticholinergics, sedatives, opioids, antipsychotics, and antiseizure drugs as contributors to dementia symptoms. Also, check if drugs like digoxin, NSAIDs, $H_2$ receptor antagonists, amiodarone, antihypertensives, and corticosteroids could contribute to delirium.
- The Folstein Mini-Mental State Examination (MMSE) can help establish a history of deficits in two or more areas of cognition at baseline against which to evaluate change in severity over time. The average expected decline in an untreated patient is 2–4 points per year (**Table 50-1**). The MMSE is copyrighted and therefore, if used, requires payment by the user. Other assessment scales are also available.
- In 2024, a revised criteria for diagnosis and staging of AD were published which incorporate developments in biomarker research.

## TREATMENT

- Goals of Treatment: To maintain cognitive functioning and activities of daily living as long as possible, with a secondary goal to treat the psychiatric and behavioral symptoms.

### NONPHARMACOLOGIC THERAPY

- Identify possible causes of cognitive and noncognitive symptoms and adjust the caregiving environment to address them.
- Manage sleep disturbances, wandering, incontinence, agitation, and aggression with behavioral and environmental interventions, like redirecting attention and removing stressors.
- At diagnosis, educate the patient and caregiver on illness progression, available treatments, legal decisions, necessary lifestyle changes, and other quality-of-life issues.
- Primary prevention includes smoking cessation, increasing physical activity, and reducing midlife obesity, hypertension, and diabetes.

### PHARMACOLOGIC THERAPY OF COGNITIVE SYMPTOMS

- Consider the antiamyloid monoclonal antibody (mAb) **lecanemab** or **donanemab** for mild cognitive impairment (MCI). Titrate to the recommended maintenance dose as tolerated.
- In mild to moderate AD, consider a cholinesterase inhibitor (**donepezil**, **rivastigmine,** or **galantamine**) or an mAb titrated to the recommended maintenance dose as tolerated.
- In moderate to severe AD, consider adding the antiglutamatergic agent **memantine** titrated to the recommended maintenance dose as tolerated; alternatively, consider memantine or cholinesterase inhibitor therapy alone.
- A reasonable response may be a slowed decline in abilities and delayed long-term care placement.
- Simplify dosing regimens, considering patient and caregiver preferences to improve medication adherence and persistence.
- Treatment gaps may be associated with a loss of benefits when medication is stopped but this is controversial.
- Behavioral symptoms may require additional pharmacologic approaches.

#### Cholinesterase Inhibitors

- **Table 50-2** summarizes cholinesterase inhibitor dosing. **Donepezil**, **rivastigmine,** and **galantamine** are indicated in mild to moderate AD; donepezil is also indicated for severe AD.

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- Duration of the benefit lasts 3–24 months.
- If rivastigmine or galantamine is interrupted for several days or longer, restart at the lowest dose due to their short half-lives. Gradual dose titration over months improves tolerability. A washout period is recommended when switching agents.
- **Table 50-3** lists common medication adverse effects and monitoring parameters. Abrupt discontinuation can worsen cognition and behavior in some patients.

TABLE 50-2

**Dosing of Medications Used for Cognitive Symptoms**

| Medication | Initial Dose | Usual Range | Dosage Adjustments |
|---|---|---|---|
| **Cholinesterase Inhibitors** | | | |
| *Donepezil* | 5 mg daily in the evening (oral)<br>5–10 mg/day (transdermal patch) applied weekly | 5–10 mg daily (mild to moderate AD)<br>10–23 mg daily (moderate to severe AD) | No dosage adjustments recommended |
| Comments: Available as: tablet, ODT, oral solution, transdermal patch; can be taken with or without food; GI adverse effects (including weight loss) are higher with 23-mg dose; therapy interruptions require retitration of dose; store transdermal patch in fridge | | | |
| *Galantamine* | 4 mg twice daily (tablet, oral solution)<br>8 mg daily in the morning (extended-release capsule) | 8–12 mg twice a day (tablet, oral solution)<br>16–24 mg (extended-release capsule) | Moderate renal or hepatic impairment: 16 mg max daily dose<br>Not recommended in severe renal or hepatic impairment |
| **Comments:** Available as a tablet, oral solution and extended-release capsule; take with meals | | | |
| *Rivastigmine* | 1.5 mg twice daily (capsule, oral solution)<br>4.6 mg/day (transdermal patch) | 3–6 mg twice a day (capsule, oral solution)<br>9.5–13.3 mg/day (transdermal patch) | Use lower oral doses for renal impairment, hepatic impairment, or low body weight (<50 kg [<110 lb]); maximum transdermal dose of 4.6 mg/24 hours for mild to moderate hepatic impairment or low body weight |
| **Comments:** Available as capsule, oral solution, transdermal patch; retitrate dose if therapy interruptions; take with meals; also indicated for mild-to-moderate dementia associated with Parkinson disease; using multiple patches together associated with hospitalization and death | | | |
| ***N*-Methyl-D-Aspartate (NMDA) Receptor Antagonist** | | | |
| *Memantine* | 5 mg daily (tablet, oral solution)<br>7 mg daily (extended-release capsule) | 10 mg twice daily<br>28 mg daily (extended-release capsule) | Severe renal impairment: 5 mg twice daily (tablet, oral solution) or 14 mg daily (extended-release capsule); administer with caution in severe hepatic impairment |
| **Comments:** Available as a tablet, oral solution, extended-release capsule; can take with or without food; can sprinkle capsule contents on applesauce for administration; therapy interruptions require dose retitration | | | |
| **Cholinesterase Inhibitor + NMDA Receptor Antagonist** | | | |
| *Memantine + donepezil* | 7 mg/10 mg (if patient is stabilized on donepezil and not currently on | 28 mg/10 mg daily | Severe renal impairment: 14 mg/10 mg daily |

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| | | | |
|---|---|---|---|
| | memantine)<br>28 mg/10 mg (if patient is stabilized on memantine and donepezil) | | |
| **Comments:** Available as memantine extended-release and donepezil capsule; retitrate dose if therapy interruptions; can take with or without food; can sprinkle capsule contents on applesauce for administration | | | |
| **Antiamyloid Monoclonal Antibody** | | | |
| *Donanemab* | 700 mg IV over 30 minutes | 700 mg IV every 4 weeks × 3 doses, then 1400 mg every 4 weeks | Has not been studied; no dosage adjustments recommended |
| **Comments:** Available as 350 mg/20 mL single-dose vials; dilute to 4–10 mg/mL with 0.9% NaCl prior to administration | | | |
| *Lecanemab-irmb* | 10 mg/kg IV solution | 10 mg/kg every 2 weeks | Has not been studied; no dosage adjustments recommended |
| **Comments:** Available as 200 mg/2 mL and 500 mg/5 mL single-dose vials; dilute with 250 mL of 0.9% NaCl and administer over ~1 hour | | | |

GI, gastrointestinal; IV, intravenous; NaCl, sodium chloride; ODT, orally disintegrating tablet.

TABLE 50-3

**Adverse Medication Effect Monitoring**

| Adverse Effect | Monitoring | Comments |
|---|---|---|
| *Cholinesterase inhibitors* | | |
| Dizziness, syncope, bradycardia, atrial arrhythmias, sinoatrial and atrioventricular block, myocardial infarction | Report of dizziness or falls, pulse, blood pressure, and postural blood pressure change | Dizziness is generally mild, transient, and unrelated to cardiovascular issues. Check pulse at baseline, monthly during titration, and every 6 months thereafter. |
| Nausea, vomiting, diarrhea, anorexia, weight loss | Weight and GI complaints | Take with food to reduce GI upset which is often transient and dose-related. Frail or low body weight patients may experience more GI effects and significant weight loss, especially with rivastigmine or with donepezil 23 mg. Transdermal rivastigmine causes fewer GI effects than oral. |
| *Donepezil* | | |
| Peptic ulcer disease, GI bleeding | Signs or symptoms of active or occult GI bleeding | Increased concern for patients at higher risk of ulcers (ie, history of ulcers or using NSAIDs). |
| Insomnia, vivid/abnormal dreams, nightmares | Sleep disturbances, daytime drowsiness | Donepezil can be taken in the morning to decrease risk |

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| | | |
|---|---|---|
| *Galantamine* | | |
| Serious skin reactions include Stevens–Johnson syndrome and acute generalized exanthematous pustulosis. | Appearance of skin rash | Discontinue at the first sign of a skin rash unless clearly unrelated. If signs suggest a serious reaction, consider alternative treatment and avoid rechallenge. |
| *Rivastigmine* | | |
| Allergic dermatitis | Reaction beyond patch size, more intense local reaction (increasing erythema, edema, papules, vesicles), and symptoms persisting over 48 hours after patch removal. | Discontinue if disseminated allergic dermatitis arises. Patients sensitized by patches may not tolerate oral rivastigmine; allergy testing and close supervision are recommended. |
| *Memantine* | | |
| Headache, confusion, dizziness, hallucinations | Report of dizziness or falls, hallucinations | Confusion may be observed during dose titration and is usually transient |
| Constipation | GI complaints | May mitigate cholinesterase inhibitor GI effects |
| *Donanemab* and Lecanemab | | |
| ARIA | Perform a baseline MRI and before the second, third, fourth, and seventh infusions. If ARIA appears, treatment depends on type, severity, and symptoms. ARIA symptoms include headache, confusion, visual changes, dizziness, nausea, gait difficulty, and rarely seizures. | Monitor for ARIA and focal neurologic changes during the first seven doses (14 weeks). *APOE*4* homozygotes have a higher risk of ARIA-related effects. |
| Infusion-related reactions | Fever, flu-like symptoms, nausea, vomiting, hypo- and hypertension, oxygen desaturation | Most occurred with the first infusion. Manage by reducing the infusion rate or discontinuing. Consider antihistamines, NSAIDs, acetaminophen, or corticosteroids before future infusions. |

ARIA, amyloid-related imaging abnormalities; GI, gastrointestinal; MRI, magnetic resonance imaging; NSAIDs, nonsteroidal anti-inflammatory drugs.

### *N*-Methyl-D-Aspartate (NMDA) Receptor Antagonist

- **Memantine** is used alone and with a cholinesterase inhibitor for moderate to severe AD, not mild AD. It is not metabolized but requires dose adjustments in renal impairment. It is usually well tolerated; adverse reactions are outlined in **Table 50-3**.
- Combination therapy with cholinesterase inhibitors and memantine, individually or as **Namzaric**, is used for moderate to severe AD. It slows cognitive and functional decline more effectively than cholinesterase inhibitor monotherapy or no treatment. Memantine may mitigate some GI effects of cholinesterase inhibitors.

### Antiamyloid Monoclonal Antibody

- Three humanized, immunoglobulin G1 mAbs are available and have been designated as AD breakthrough therapies by the FDA (ie, lecanemab,

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donanemab, and gantenerumab).

- Dosing for these is outlined in **Tables 50-2** and **50-3**, discuss adverse effects.
- The potential degree and duration of clinical benefit of antiamyloid antibodies remains largely unclear.

### Other Medications

- Use of estrogen, NSAIDS, prednisone, and statins is not recommended to prevent or treat dementia.
- Dietary supplements (vitamin E, vitamin B, Ginkgo biloba) aren't recommended for treatment. Avoid Ginkgo biloba in individuals on anticoagulants or antiplatelets, and use cautiously with NSAIDs.
- There is insufficient evidence to recommend omega-3 fatty acids or medical foods such as Axona, Souvenaid, and Cerefolin NAC for treating AD.

## PHARMACOLOGIC THERAPY OF NEUROPSYCHIATRIC SYMPTOMS

- Guidelines include: (1) reserve for when nonpharmacologic therapies fail; (2) start with reduced doses, titrate slowly; (3) monitor closely; (4) periodically taper and discontinue; (5) document carefully.
- Cholinesterase inhibitors and memantine may help treat behavioral and psychological symptoms but don't reduce acute agitation. Avoid anticholinergic medications as they may worsen cognition.

### Antidepressants

- Antidepressants may help manage anxiety, apathy, as well as agitation and aggression.
- A selective serotonin reuptake inhibitor (SSRI) can be used to treat depression, with the best evidence for **sertraline** and **citalopram**. Tricyclic antidepressants are usually avoided.

  ✓ Common SSRI adverse medication reactions can be found in Chapter 67.

### Antipsychotics

- Brexpiprazole is FDA-approved for managing agitation in dementia due to AD. Start at 0.5 mg, titrating weekly to 2 mg daily. It may take 4+ weeks to see improvement.
- Antipsychotic medications are traditionally used for psychotic and hyperactive symptoms, but risks and benefits must be carefully weighed.
- Second-generation antipsychotics (**aripiprazole, risperidone, olanzapine, quetiapine**) are more effective than placebo, but higher risks of adverse effects and mortality offset benefits. They should be restricted to severe, unresponsive symptoms. Taper treatment early, rarely use beyond 12 weeks.

  ✓ Common adverse effects include somnolence, extrapyramidal symptoms, abnormal gait, worsened cognition, cerebrovascular events, and increased risk of death (black-box warning). See Chapter 70 for more information.

### Miscellaneous Therapies

- Evidence for benzodiazepine use is lacking and is not advised due to significant adverse medication reactions.
- Use of antiseizure medications (also known as mood stabilizers), **carbamazepine, lamotrigine, pregabalin,** and **gabapentin,** may be alternatives for agitation, but evidence is conflicting.
- Use of **valproic acid** is no longer recommended due to severe adverse effects.

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## EVALUATION OF THERAPEUTIC OUTCOMES

- At baseline, interview both patient and caregiver to identify target symptoms, define goals, and document cognitive and physical status, performance, mood, thoughts, and behavior.
- Use a validated scale to assess cognition, daily activities (eg, Bristol Activities of Daily Living Scale), and behavioral issues (eg, Neuropsychiatric Inventory Questionnaire) to measure symptom changes and functioning.
- Carefully observe medication efficacy, need for dose adjustments, adherence, potential adverse reactions, and document monitoring method and frequency.
- Make medication changes at 2–4 and 8–12 weeks after starting, then reassess every 3–6 months. It may take several months to a year to assess cognitive medication benefits.
- Deprescribing medications for AD is supported by available guidelines. The decision on when to stop treatment due to lack of efficacy is controversial.

*See Chapter 77, Alzheimer Disease, authored by Ericka L. Crouse, Kristin M. Zimmerman, Emily P. Peron, Lana J. Sargent, and Sarah E. Hobgood, for a more detailed discussion of this topic.*

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